



The effect of acutely administered MDMA on subjective and BOLD-fMRI responses to favourite and worst autobiographical memories

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Abstract

3,4-methylenedioxymethamphetamine (MDMA) is a potent monoamine-releaser that is widely used as a recreational drug. Preliminary work has supported the potential of MDMA in psychotherapy for post-traumatic stress disorder (PTSD). The neurobiological mechanisms underlying its putative efficacy are, however, poorly understood. Psychotherapy for PTSD usually requires that patients revisit traumatic memories, and it has been argued that this is easier to do under MDMA. Functional magnetic resonance imaging (fMRI) was used to investigate the effect of MDMA on recollection of favourite and worst autobiographical memories (AMs). Nineteen participants (five females) with previous experience with MDMA performed a blocked AM recollection (AMR) paradigm after ingestion of 100 mg of MDMA-HCl or ascorbic acid (placebo) in a double-blind, repeated-measures design. Memory cues describing participants' AMs were read by them in the scanner. Favourite memories were rated as significantly more vivid, emotionally intense and positive after MDMA than placebo and worst memories were rated as less negative. Functional MRI data from 17 participants showed robust activations to AMs in regions known to be involved in AMR. There was also a significant effect of memory valence: hippocampal regions showed preferential activations to favourite memories and executive regions to worst memories. MDMA augmented activations to favourite memories in the bilateral fusiform gyrus and somatosensory cortex and attenuated activations to worst memories in the left anterior temporal cortex. These findings are consistent with a positive emotional-bias likely mediated by MDMA's pro-monoaminergic pharmacology.

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Introduction

3,4-methylenedioxymethamphetamine (MDMA) is a hybrid stimulant/psychedelic drug with unique subjective and pharmacological properties. MDMA stimulates serotonin (5-HT), dopamine and noradrenaline release in the synapse but its marked pro-serotonergic effects distinguish it from other amphetamines (Rothman et al., 2001) and define its unique psychological profile. MDMA has been described as an 'empathogen' and it is known to promote social interaction, positive emotion

and openness (Bedi et al., 2010). Preliminary work indicates that MDMA may be effective for assisting psychotherapy for refractory post-traumatic stress disorder (PTSD) (Mithoefer et al., 2011, 2013). In this context, it is hypothesised to reduce the fear-response, allowing patients to revisit traumatic memories in a supportive setting, without feeling overwhelmed (Greer and Tolbert, 1998; Mithoefer et al., 2011). The neurobiological mechanisms underlying these putative effects are, however, poorly understood. There have been a limited number of small-scale functional magnetic resonance imaging (fMRI) studies on the acute effects of MDMA (Bedi et al., 2009; Ramaekers et al., 2009; Kuypers et al., 2011) and only one that has overt implications for its therapeutic use: reduced amygdala responses to angry faces was observed under MDMA (Bedi et al., 2009), broadly consistent with reduced fear. The positive mood effects of MDMA appear to be mediated by stimulation of the

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serotonin 2A receptor (5-HT_{2AR}) – likely via increased synaptic 5-HT (Liechti *et al.*, 2000; van Wel *et al.*, 2012). However, other receptors are also involved (Liechti and Vollenweider, 2001).

Previous fMRI studies of autobiographical memory recollection (AMR) have identified a core autobiographical memory (AM) system incorporating the retrosplenial cortex (RSP), medial prefrontal cortex (mPFC), medial temporal lobes (MTLs), temporoparietal junction and the lateral temporal cortex (Svoboda *et al.*, 2006). Some of these have found increased responses in the AM system during recollection of positive relative to negative personal memories (Piefke *et al.*, 2003; St Jacques *et al.*, 2011), whereas recollecting negative memories engages executive regions, such as the dorsal and lateral PFC (Anderson *et al.*, 2004). There is a rich literature on neuronal responses to trauma-related memory scripts in patients with PTSD. The most consistent finding is increased amygdala and reduced mPFC responses in patients relative to controls (Lanius *et al.*, 2011); however, increased mPFC responses have also been observed in patients with dissociative symptoms (Lanius *et al.*, 2012).

We previously investigated the effects of the pro-serotonergic hallucinogen, psilocybin, on autobiographical memory recollection, and found increased activations in high-level visual regions under the drug (Carhart-Harris *et al.*, 2012). This study used only positive memory cues however, and no studies have simultaneously investigated the effects of a psychoactive drug on recollection of both emotionally positive and negative personal memories. This knowledge gap is important to bridge, as psychotherapy often involves recall of both positive and negative personal experiences (Brewin, 2006; Rauch *et al.*, 2012). Previous research found a reduced sensitivity to threat-related stimuli (Bedi *et al.*, 2010; Hysek *et al.*, 2012) and an increased sensitivity to positive stimuli under MDMA (Hysek *et al.*, 2012), broadly consistent with increased serotonergic functioning (Harmer, 2008; Murphy *et al.*, 2009; Tranter *et al.*, 2009). Reduced sensitivity to threat-related stimuli may be useful in exposure therapy – an effective treatment for PTSD that requires patients re-engage with traumatic memories in order to overcome them (Rauch *et al.*, 2012). The key rationale for using MDMA in conjunction with exposure therapy is that it allows the patient to more easily engage with traumatic material (Mithoefer *et al.*, 2013).

The present study employed an fMRI protocol in which healthy participants were presented with personalised autobiographical memory cues designed to evoke their favourite and worst personal memories. Participants viewed a different set of memories after oral administration of placebo (100 mg ascorbic acid) and MDMA-hydrochloride (HCl) (100 mg) and associated hemodynamic responses were estimated using blood oxygenation level dependent imaging (BOLD) imaging and general linear modelling. We predicted that MDMA would reduce BOLD and subjective responses to negative

memories and augment responses to positive memories, consistent with a positive emotional bias mediated by increased serotonergic functioning (Hysek *et al.*, 2012).

Methods

Design

Participants were enrolled in a within-subjects, double-blind, randomised, placebo-controlled study and scanned twice, 7 d apart, once after MDMA and once after placebo. The study was approved by National Research Ethics Service (NRES) West London Research Ethics Committee, Imperial College London's Joint Compliance and Research Office, Imperial College Healthcare NHS Trust and Imperial College London's Faculty of Medicine, and was conducted in accordance with Good Clinical Practice guidelines. A Home Office Licence was obtained for the storage and handling of a Schedule 1 drug and Imperial College London sponsored the research.

Participants

The study sample comprised 19 healthy participants (mean age 29.4±7.4, 5 females). Two participants were removed from the fMRI analyses owing to failure to follow task instructions (including staying sufficiently still in the scanner and opening and closing their eyes when instructed to do so). One additional subject did not complete the memory task because of a technical issue with the presentation software. None of the participants had used MDMA for at least 7 d and other drugs for at least 48 h, and this was confirmed by a urine screen. An alcohol breathalyser test confirmed that none of the participants had recently consumed alcohol. The 19 participants included in the subjective analysis had used MDMA an average of 40.7 (±58) times before (range=1 to 200) and the mean time since last use was 897 (±1751) d (range=7 to 6500 d). Participants were screened for general health, magnetic resonance (MR)-compatibility and present mental health. Inclusion criteria were presently mentally and physically healthy as determined by a psychiatric interview and medical screen and at least one previous experience with MDMA. Medical screening involved routine blood tests, electrocardiogram, heart rate, blood pressure and a brief neurological exam.

For the sample of 19, other drug use parameters were as follows (values are mean±S.D. (range)): alcohol weekly units 11.2±9.6 (0–30), daily cigarettes 1.6±4.7 (0–20), cannabis lifetime uses 325.8±351 (0–1000+), lysergic acid diethylamide (LSD) lifetime uses 37.1±118 (0–500), psilocybin lifetime uses 11.4±23 (0–100), ketamine lifetime uses 24.4±50.5 (0–200), mephedrone lifetime uses 4.8±8.4 (0–30), amphetamine lifetime uses 18±41.5 (0–150), cocaine lifetime uses 24.7±50.3 (0–200). Participants had mean Beck Depression Inventory (BDI) scores of 3.3±5.3 (0–18) and State-Trait Anxiety

Inventory (STAI) scores of 32 ± 6 (20–46). The participant with the BDI score of 18 was deemed well enough to participate based on a thorough psychiatric interview.

Filmed participants

An additional five participants were filmed as part of a UK television documentary (Channel 4[®]) on the effects of MDMA; however, these participants' data have been excluded from the present analyses. Thus, only data from non-filmed participants are reported here.

Scanning parameters

MR images were acquired on a 3T Siemens Tim Trio (Siemens Healthcare, Germany) using a 32-channel phased array head coil. Anatomical reference images were acquired using the Alzheimer's Disease Neuro-imaging Protocol Grand Opportunity (ADNI-GO) recommended magnetization-prepared rapid gradient-echo (MPRAGE) parameters (1 mm isotropic voxels, repetition time (TR)=2300 ms, echo time (TE)=2.98 ms, 160 sagittal slices, 256×256 in-plane resolution, flip angle=9 degrees, bandwidth=240 Hz/pixel, generalized autocalibrating partially parallel acquisitions (GRAPPA) acceleration=2). T2*-weighted echo-planar images (EPI) were acquired for the functional task using 3 mm isotropic voxels in a 192 mm in-plane field of view (FOV), TR=2 s, echo time =31 ms, 80 degree flip angle, 36 axial slices in each TR, bandwidth=2298 Hz/pixel, and a GRAPPA acceleration of 2. During the functional imaging paradigm, 562 volumes were acquired, which took 18 min and 44 s to complete.

Derivation of autobiographical memory cues

Participants were instructed at screening to provide 12 short autobiographical memory cues referring to 12 separate emotionally salient personal memories. They were asked to compile two lists of six memories: one containing six of their very best memories (favourite memories) and another containing six of their very worst. They were instructed that the cues should refer to specific life events rather than prolonged periods of time in their lives. They were advised that the cues should be brief (i.e. no longer than one short sentence) and abridged such that they cannot be understood by others (e.g. 'remember X in TPG'). This proved an effective strategy as it ensured participants chose memories without fear of social judgement, thus avoiding that potential confound. However, not all subjects felt the need to encrypt their cues in this way. Examples of other cues included: 'remember the waterfall' (favourite) and 'remember being told my friend was dead' (worst). Participants were asked to rank each memory in terms of its 'potency', i.e. its capacity to evoke a strong emotional response. The 12 memories were split into two lists of six, each containing three favourite and three worst memories. This was

done so that a fresh set of memories were viewed under placebo and MDMA, thus avoiding habituation effects. The two lists were balanced for potency across conditions, using the pre-scanning rankings of potency. Specifically, ranks 1, 4 and 6 were used in one scan and 2, 3 and 5 in the other, and the order of this split was counterbalanced so that 50% of the sample had ranks 1, 4 and 6 in scan 1 and 50% had these in scan 2.

Drug and dosing parameters

Participants began the autobiographical memory task 80–85 min after oral administration of 100 mg encapsulated MDMA-HCl and on a separate occasion, placebo (100 mg encapsulated ascorbic acid/vitamin-C). Peak subjective effects were reported 70–100 min post administration, roughly consistent with the plasma t-max of MDMA (Kolbrich et al., 2008). The order of MDMA and placebo administration was counterbalanced so that an equal number of participants received placebo first as MDMA. The 100 mg dose compares well with previous acute administration studies. MDMA is well tolerated at doses between 75–100 mg (de la Torre et al., 2004; Bedi et al., 2009).

Functional imaging paradigm

Eighteen memory cues were presented in a blocked design (three favourite memories and three worst memories, three repetitions of each) interleaved with an auditory attention task and a task-free 'rest' period (Carhart-Harris et al., 2012). There was only one continuous run of the task. In brief, participants were visually presented with an autobiographical memory cue for 5 s (e.g. 'remember being told my friend was dead') followed by the visual instruction: 'close your eyes' which was presented for 13 s, after which there was a pre-recorded auditory instruction: 'open your eyes'. Participants were then visually presented with the instruction: 'count the tones' for 5 s, followed by the visual instruction: 'close your eyes'. For 13 s, the participants heard 13 auditory tones (1 per second) of one of two pitches, either high or low, after which they heard: 'open your eyes' and were visually presented with the question: 'were there more high or low tones?' Participants gave a response via button press using their index ('more low') or middle ('more high') finger. They were then visually presented with the instruction: 'relax' which appeared for 5 s, followed by: 'close your eyes'. After a rest period of 13 s, participants heard the auditory instruction: 'open your eyes'. The sequence outlined above was repeated 18 times in total. An autobiographical recollection trial was always followed by an auditory attention trial; thus, forcing a suspension of recollection. Participants were instructed to recall their memories as vividly as possible during the eyes-closed period after the memory cue.

Subjective ratings

After exiting the scanner, participants gave VAS-style subjective ratings for each of the six memories they had just viewed, i.e. single lines were placed on each scale with anchors at either end. The scales were continuous. Four items were rated for each memory, presented in the following way: (1) 'How strong were the emotions you felt for this memory?' From: 'I felt no real emotion' to: 'Really strong!' (2) 'How vivid were your recollections of this memory?' From: 'Really vague' to: 'Really vivid, as if I was reliving it!' (3) 'How positive were the emotions you felt for this memory?' From: 'It wasn't positive at all' to: 'Really positive!' (4) How negative were the emotions you felt for this memory? From: 'It wasn't negative at all' to: 'Really negative'.

Imaging analysis

All analyses were performed using the neuroimaging software SPM8 (<http://www.fil.ion.ucl.ac.uk/spm>) using standard parameters and procedures. The raw three-dimensional (3D) image files were realigned, co-registered and normalised to a standard T1 image template, and finally smoothed using an 8 mm Gaussian kernel. Processed images were entered into a General Linear Model (GLM) and blocked epochs were modelled as boxcar functions and convolved with the hemodynamic response function. Six motion regressors were entered and a high-pass filter of 240 s applied. The baseline was defined as the 13 s eyes-closed rest period and this was contrasted against the eyes-closed recollection periods for favourite and worst memories and all of the relevant second-level analyses reported here included AMR (i.e. favourite and worst either separately or combined) *vs.* rest as the first-level contrast parameter estimates. Second-level, mixed-effects analyses were performed to calculate the effect of AMR at the within and between-condition (placebo and drug) levels. All higher-level analyses used a cluster-corrected statistical threshold of $p < 0.05$, with a minimum cluster size of 250 voxels.

Results

Subjective effects

Participants rated their favourite memories as significantly more positive ($p=0.008$), vivid ($p=0.00003$) and emotional ($p=0.001$) after MDMA compared with placebo and their worst memories were rated as significantly less negative after the drug ($p=0.049$, Fig. 1).

Functional MRI results

BOLD responses during autobiographical memory recollection

Two subjects showed mean movement in excess of one voxel (3 mm) and were removed from the analysis, giving a sample size of 17 for the imaging analyses. Robust

activations and deactivations were observed during AMR (collapsing memory valence and condition, Fig. 2). Activations were significant in regions classically associated with AMR such as the hippocampus, parahippocampal gyrus and retrosplenial cortex, but also in the pre-supplementary motor area/dorsal anterior cingulate cortex, bilateral ventral and dorsal prefrontal cortex, caudate nucleus, bilateral insula, cerebellum and temporal pole. Deactivations were observed in the dorsal posterior cingulate cortex, precuneus and ventral visual association regions (see Table 1 for significant clusters).

Effect of memory valence

Activations to favourite memories (*vs.* rest) were compared against activations to worst memories (*vs.* rest), collapsing across conditions. Results revealed significantly greater activations in the bilateral parahippocampal gyrus during recollection of favourite memories *vs.* recollection of worst memories (Fig. 3a). Conversely, significantly greater activations were observed in the superior frontal gyrus/dorsal mPFC, superior temporal gyrus and left and right early visual cortex to worst memories than favourite (Fig. 3b).

Effects of MDMA on BOLD responses during AMR

The effect of MDMA on recollection of favourite and worst memories was analysed separately. MDMA augmented activations to favourite memories in five clusters: bilaterally in the fusiform gyrus, the right postcentral gyrus (primary somatosensory cortex), left middle temporal gyrus and left inferior parietal lobe (Fig. 4a, Table 1). There were no regions in which activations to favourite memories were greater under placebo. Conversely, left anterior temporal lobe activations to worst memories were reduced under MDMA (Fig. 4b, Table 1) and no regions showed greater responses to worst memories under MDMA.

Correlations between responses in regions showing a modulatory influence of MDMA and subjective ratings

All correlational analyses were restricted to the MDMA condition to avoid forcing positive outcomes (i.e. there were 17 data points in each correlation). There was a significant positive correlation between activations in the left anterior temporal lobe (LATL) to worst memories and ratings of negative emotion felt upon their recollection ($p=0.00004$, $R^2=0.65$, Fig. 5). After correcting for multiple comparisons (Bonferroni), there were no significant correlations between BOLD response in the clusters that showed an augmented response to favourite memories under MDMA and ratings of memory vividness, emotional intensity or positive emotion. However, there was a trend positive correlation between responses in the left middle temporal gyrus and ratings of recollection vividness ($p=0.02$, $R^2=0.24$).

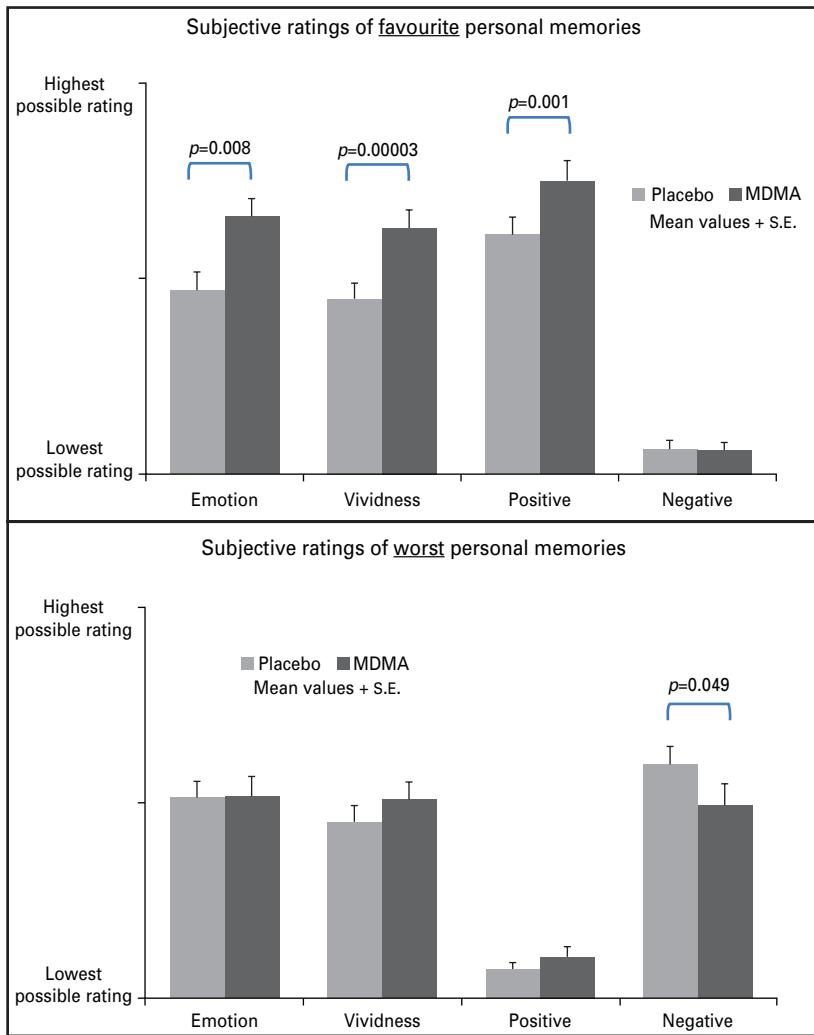


Fig. 1. Subjective ratings of autobiographical memories: Displayed are the mean ratings (+s.e.) for each item after placebo (light grey) and 3,4-methylenedioxymethamphetamine (MDMA) (dark grey). *p* values are shown for significant results. Paired *t* tests, *p*<0.05, *n*=19. LH: left hemisphere; RH: right hemisphere.

Discussion

This study sought to investigate the effect of MDMA on recollecting emotionally potent personal memories in order to inform how the drug may be useful in psychotherapy (Mithoefer et al., 2011, 2013). The primary hypotheses of the study concerned the effect of MDMA on recollecting memories of different emotional valence (i.e. Figs. 1 and 4). Participants reported experiencing their favourite memories as more vivid, emotionally intense and positive after MDMA than placebo – reflecting a marked intensification of emotionally positive memories (Fig. 1). For example, one participant reported: ‘With the drug, positive memories seemed much more intense and real.’ And another: ‘On the drug, good memories were more intense and especially made me feel positive emotions’. There was also a significant increase in activations to favourite memories in the ventral visual and somatosensory cortices after MDMA (Fig. 4a).

Previous work has found a relationship between hippocampal responses during AMR and the strength of emotion felt upon recollection (Svoboda et al., 2006; Carhart-Harris et al., 2012) as well as visual cortex responses during AMR and recollection vividness (Daselaar et al., 2008; Carhart-Harris et al., 2012) and preferential responses to positive memories were observed in bilateral hippocampal clusters in the present study. Increased hippocampal responses to positive AMs under MDMA were not observed in the present study; however, there were significantly increased responses in the bilateral fusiform gyri under the drug (Fig. 4a). The fusiform gyrus is known to be involved in processing high-level visual stimuli such as faces (Weiner and Grill-Spector, 2012). Thus, increased fusiform gyrus activations under MDMA may relate to the reports of increased recollection vividness under the drug – particularly since many of the favourite memories contained references to people. Similarly, several of the positive memory cues

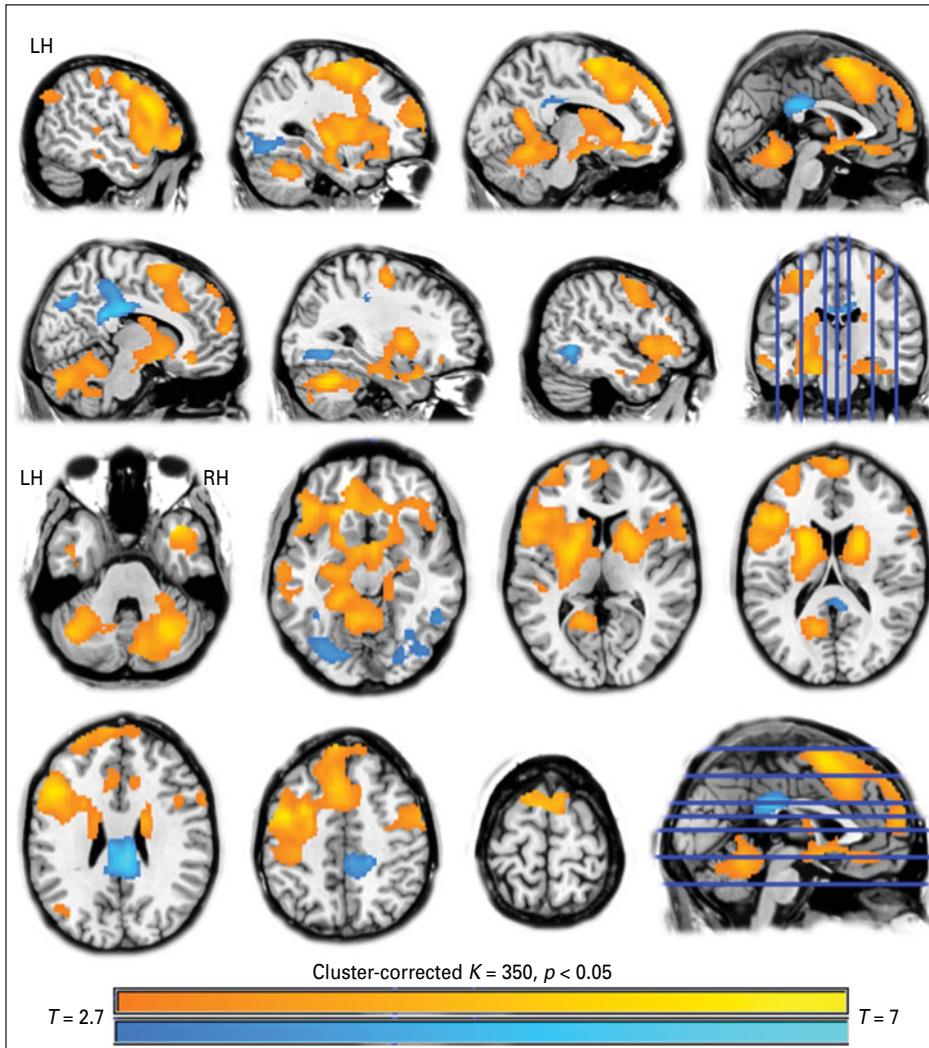


Fig. 2. Hemodynamic responses during autobiographical memory recollection (AMR): (a) Slices showing significant activations and deactivations during AMR for the sample of 17 participants, with the placebo and 3,4-methylenedioxymethamphetamine (MDMA) conditions and memory valence combined. Activations *vs.* resting baseline are displayed in orange and deactivations in blue. All clusters were significant at a cluster-corrected threshold of $p < 0.05$, cluster-size > 350 voxels. The blue lines on the brain shown in the bottom right indicate the planar position of the presented slices. LH: left hemisphere; RH: right hemisphere.

referred to sensual experiences and these may have been felt with enhanced vividness under MDMA given the increased somatosensory cortical activations. Further work is required to test the reliability of these inferences.

Perhaps more relevant to the potential application of MDMA in psychotherapy for PTSD, participants reported experiencing their worst memories as significantly less negative under MDMA (Fig. 1). Together with the subjective intensification of favourite memories, this attenuation of negative affect during the recollection of worst memories reflects a positively-biased shift in emotional processing that is broadly consistent with increased serotonergic functioning (Harmer, 2008) and previous MDMA studies (Bedi et al., 2009, 2010; Hysek et al., 2012). For example, one participant reported: 'The bad memories were less salient [under MDMA]

and I thought about them in a matter of fact way.' And another: 'When I reached back for the bad memories [under MDMA] they did not seem as bad; In fact, I saw them as fatalistic necessities for the occurrence of later good events.'

Significantly reduced activations to worst memories were observed in the left anterior temporal cortex or temporal pole (Fig. 4b). Moreover, when the BOLD amplitude data for the responses to worst memories were extracted for the MDMA condition, a significant positive correlation was found between IATL activations and ratings of negative emotion (Fig. 5). Indeed, 65% of the variance in negative affect ratings was explained by the IATL responses, supporting the inference that this specific region is involved in negative memory-evoked negative emotion. The temporal pole has been implicated in processing

Table 1. The significant clusters of activation and deactivation for all of the second-level contrasts that were carried out and reported

	Contrast	Voxels	T (peak)	p value	peak (x,y,z)	Region	Figure
Activate	All AMs						
	Cluster 1	39 574	8.05	<0.001	-42,-2,44	IMFG	2
	Cluster 2	474	5.12	0.021	-64,-38,-10	IMTG	
Deactivate	Cluster 3	421	3.78	0.029	-50,-72,38	IMOG	
	Cluster 1	1803	7.32	<0.001	6,-30,28	dPCC	
	Cluster 2	421	5.98	0.029	16,-68,42	rPREC	
	Cluster 3	1070	5.5	0.040	52,-54,-4	rMTG	
Activate	Cluster 4	753	4.44	0.005	-38,-62,-4	ISGC	
	Fav>worst						
	Cluster 1	688	5.01	0.004	-26,-34,-16	IPHG	3a
Activate	Cluster 2	816	4.33	0.002	40,-36,-8	rPHG	
	Worst>fav						
	Cluster 1	846	6.17	0.002	20,-80,-32	ICER	3b
	Cluster 2	1802	6.08	<0.001	-52,-60,32	rSMG	
MDMA>plac	Cluster 3	5650	5.96	<0.001	-42,-86,-2	IMOG	
	Cluster 4	933	5.46	0.001	-44,10,50	IMFG	
	Favourite						
	Cluster 1	501	4.72	0.005	60,-12,32	rPCG	4a
	Cluster 2	258	4.51	0.035	-32,-64,-14	IFG	
Plac>MDMA	Cluster 3	302	4.27	0.024	-56,-32,56	IMTG	
	Cluster 4	257	4.25	0.035	44,-36,36	IPPL	
	Cluster 5	254	3.9	0.036	32,-60,-16	rFG	
	Worst						
	Cluster 1	414	5.13	0.020	-48,0,-26	ATL	4b

MFG=middle frontal gyrus, l=left, r=right, MTG=middle temporal gyrus, MOG=middle occipital gyrus, dPCC=dorsal posterior cingulate cortex, PREC=precuneus, SGC=sub-gyral cortex, PHG=parahippocampal gyrus, CER=cerebellum, SMG=supramarginal gyrus, PCG=paracentral gyrus, FG=fusiform gyrus, IPL=inferior parietal lobe, ATL=anterior temporal lobe/temporal pole.

negative emotions before (Musser et al., 2012; Lenzi et al., 2013; Meyer et al., 2013); thus, the present result is consistent with this.

With the caveat that this study involved healthy participants and not patients, and that ratings of negative emotion were relatively low, even under placebo (i.e. few subjects reported experiencing extreme negative emotion), we can speculate that MDMA may be useful in psychotherapy for PTSD because it lessens the emotional impact of painful memories – perhaps by attenuating left anterior temporal cortical responses to them. The vividness and emotional intensity of negative memory recall was not significantly affected by MDMA, but the experience of negative affect was (Fig. 1b). This is broadly consistent with the hypothesis that MDMA enables patients with PTSD to revisit painful memories, but not in a manner that is dominated by negative affect (Mithoefer et al., 2013). Previous work found reduced amygdala responses to angry and fearful faces after MDMA (Bedi et al., 2009) and citalopram (Harmer et al., 2006; Murphy et al., 2009; Anderson et al., 2011; Godlewska et al., 2012) respectively. Thus, reduced responses to negative emotional stimuli are reliably associated with increased serotonergic functioning. The amygdala is closely involved in affective processing (Gallagher and Chiba, 1996) and the temporal

pole is proximal to and densely connected with the amygdala (Bach et al., 2011; Bickart et al., 2012). The relationship observed here between temporal pole activity and emotion may be related to its connectivity with the amygdala. This putative relationship could be interrogated further using psychophysiological interaction functional connectivity analyses (Friston et al., 1997) or dynamic causal modelling (Friston et al., 2003). For example, it might be predicted that MDMA increases functional connectivity between the anterior temporal cortex and amygdala during autobiographical memory recollection.

Together, the present results support the primary hypothesis that MDMA increases subjective and neuronal responses to favourite memories and reduces responses to worst memories. The results imply that MDMA causes a positive emotional bias, consistent with its known pro-monoaminergic and mood-promoting effects. Speculatively, the results may also be seen as broadly supportive of the application of MDMA in psychotherapy, e.g. by heightening positive affect in the context of cognitive bias modification (Macleod, 2012) or by softening the impact of painful memories (Mithoefer et al., 2011, 2013).

Drug-assisted psychotherapy is appealing for several reasons. Pharmacological treatments generally work by tempering symptoms (Cowen, 2008) but they do not

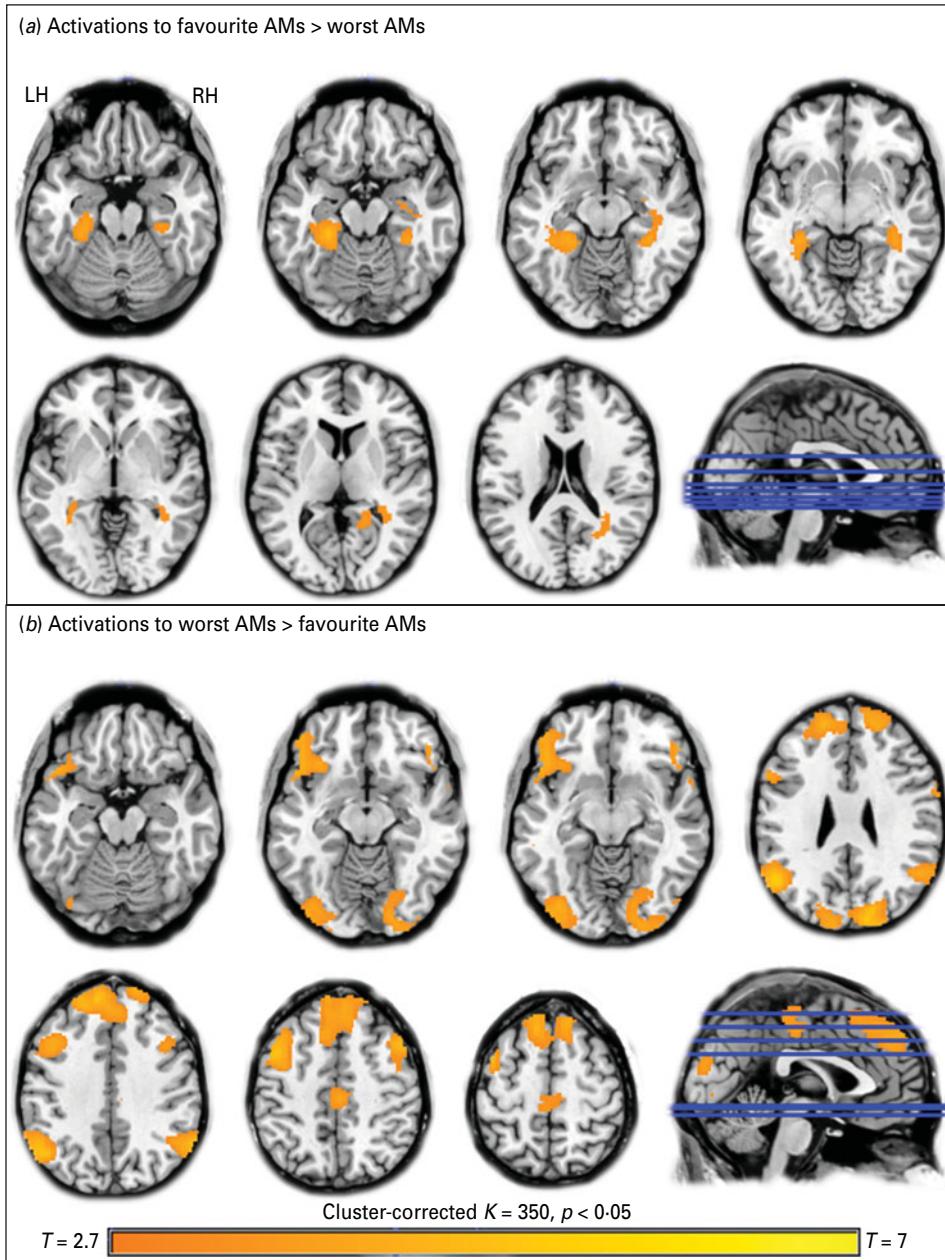


Fig. 3. (a) Regions where there were significantly greater activations to favourite memories than worst memories. (b) Regions where there were significantly greater activations to worst memories than favourite memories. 3,4-methylenedioxymethamphetamine (MDMA) and placebo conditions are combined for these analyses. All clusters were significant at a cluster-corrected threshold of $p < 0.05$, cluster size > 350 voxels. The blue lines on the sagittal slice indicate the planar position of the axial slices. LH: left hemisphere; RH: right hemisphere.

address a patient's personal history, present environment or cognitive style. Medications are typically taken chronically and chronic-use increases the risk of side-effects and places demands on treatment compliance. Psychotherapy does address environmental causes but it is a relatively expensive procedure that places significant responsibilities on patients. The appeal of drug-assisted psychotherapy relates to its potential to shorten treatment and enhance its efficacy (Sessa, 2009; Mithoefer *et al.*, 2011, 2013). MDMA-assisted psychotherapy, like classic psychedelic-assisted psychotherapy (Grob *et al.*, 2011),

typically involves a small number of drug-assisted sessions, with potentially lasting beneficial effects (Griffiths *et al.*, 2008; Grob *et al.*, 2011; Mithoefer *et al.*, 2013).

The pharmacological mechanism by which MDMA (potentially) facilitates the psychotherapeutic processes is deserving of special attention, particularly since questions remain over its neurotoxic potential, at least in higher doses (Erritzoe *et al.*, 2011). If we knew more about the pharmacological pathways through which MDMA elicits its putative therapeutic effects, then other compounds could be investigated that stimulate the

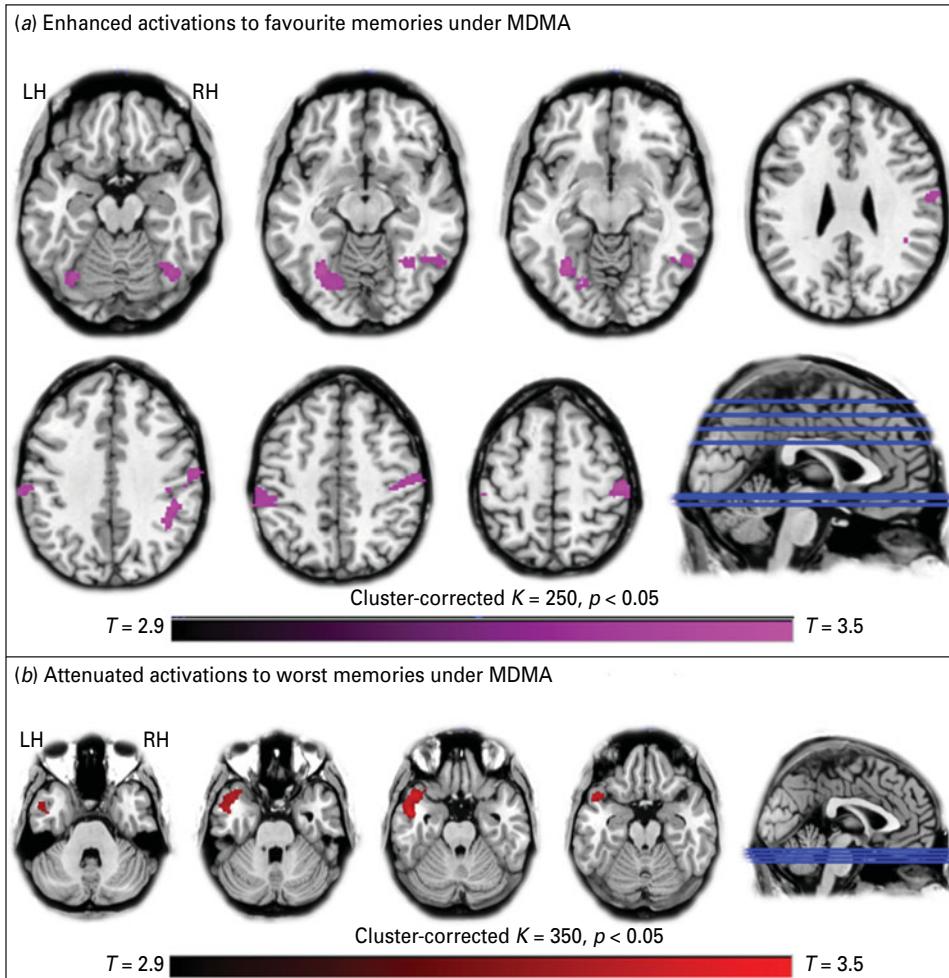


Fig. 4. (a) The effect of 3,4-methylenedioxymethamphetamine (MDMA) on activations to favourite memories. The purple colour indicates regions where there was significantly greater activation to favourite memories under MDMA than placebo. (b) The effect of MDMA on activations to worst memories. The red colour indicates regions where there was significantly less activation to worst memories under MDMA than placebo. Images are cluster-corrected, $p < 0.05$, with a minimum cluster size of 250 voxels. AM: autobiographical memory. LH: left hemisphere; RH: right hemisphere.

same pathways but with an improved toxicology (Nichols et al., 1990). It is generally assumed that the mood-improving effects of pro-serotonergic compounds, such as 5-HT reuptake inhibitors, depend on increased synaptic 5-HT stimulating postsynaptic 5-HT_{1A} receptors; however, it may be that the 5-HT_{2AR} plays an important role as well. For example, the 5-HT_{2AR} is up-regulated in 5-HT depletion states (Cahir et al., 2007; Urban et al., 2012); cortical 5-HT_{2AR} expression correlates positively with pessimistic thinking (Meyer et al., 2003a) and neuroticism (Frokjaer et al., 2008); the 5-HT_{2AR} agonist psilocybin increase subjective wellbeing (Griffiths et al., 2006), positive mood (Kometer et al., 2012) and openness (MacLean et al., 2011); and the 5-HT_{2AR} antagonist ketanserin blocks its positive mood effects (Kometer et al., 2012) and the positive mood effects of MDMA (van Wel et al., 2012). These factors imply that the 5-HT_{2AR} may be a viable target for new pharmacotherapeutics. The fact that 5-HT_{2AR} stimulation can also elicit

psychotomimetic effects should not necessarily be a deterrent, since other psychotomimetics (e.g. ketamine) are showing an impressive therapeutic potential (Duman and Aghajanian, 2012).

Given the marked positive shift in emotional valence processing seen here with MDMA, it would also be interesting to look at the relationship between MDMA and optimism bias (Sharot et al., 2011); specifically with a view to better understanding the pharmacology of this important and common behaviour. For example, given the association between the 5-HT_{2AR} and pessimism (Meyer et al., 2003b), 5-HT_{2AR}-stimulation and positive mood (Kometer et al., 2012; van Wel et al., 2012) and MDMA and positively-biased emotional valence processing (as seen here) one might predict that MDMA would accentuate the optimism bias and that this would be attenuated by antagonism of the 5-HT_{2AR}.

Finally, we should also consider the role of dopamine and oxytocin (Beringer et al., 2009; Broadbear et al.,

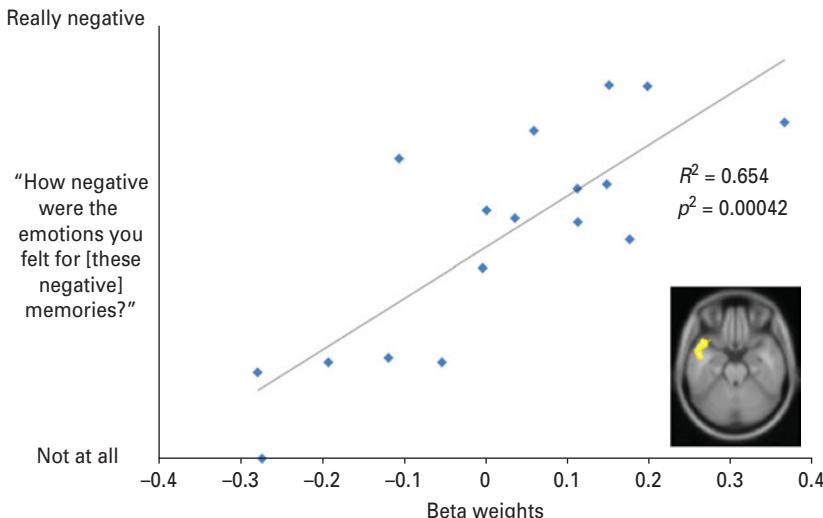


Fig. 5. Correlation between activations in the left anterior temporal lobe to worst memories under 3,4-methylenedioxymethamphetamine (MDMA) and ratings of negative emotion felt upon recollection these memories. Participants with relatively low left anterior temporal lobe/temporal pole (LATL) activation experienced less negative emotional responses to the negative memory cues.

2011) in MDMA's putative therapeutic action. It would be interesting for example to test MDMA against amphetamine, or a similar dopamine-preferring stimulant, in psychotherapy for PTSD, or to test oxytocin itself. It might also be interesting to test the efficacy of MDMA against a more widely tested psychotherapeutic adjunct such as d-cycloserine (Ressler *et al.*, 2004; Hofmann *et al.*, 2006).

Aside from the effects of MDMA on AMR, the activation maps generated by the AMR paradigm were robust and consistent with those of previous AMR fMRI studies (Svoboda *et al.*, 2006). Eyes-closed recollection *vs.* eyes-closed 'rest' is an effective design as it isolates recollection as the sole variable of interest (however, see below regarding methodological limitations). It is interesting that recollection of participants' favourite memories produced significantly greater activations in the hippocampus and parahippocampus than their worst memories (Fig. 3a). These regions are closely associated with memory recollection (Svoboda *et al.*, 2006) and participants reported their favourite memories as especially vivid, perhaps implying a greater willingness to engage with these than their worst memories (Piefke *et al.*, 2003). Similarly, participants may have over-intellectualised their worst memories or actively suppressed them, as reflected in the greater activations in executive regions, such as the superior frontal gyrus, and smaller activations in hippocampal regions to worst memories than favourite (Anderson *et al.*, 2004). The engagement of such defence mechanisms may also explain the generally relatively low ratings of negative emotion during worst memory recollection.

There are several limitations to this study. One of the most important is that the study involved healthy volunteers and not patients with PTSD. Further work is

required to validate the AMR procedure used in this study as a model of an aspect of psychotherapy relevant to the treatment of PTSD. That we used healthy volunteers and not patients therefore limits our ability to extrapolate between the two. Some of the participants in the present study provided memories that were of an overtly distressing nature (e.g. sudden unexpected bereavements and physical and sexual assaults); however, screening did not reveal any current symptoms of PTSD. Patients with PTSD may encode and retrieve traumatic memories via mechanisms that are unique or specific to their pathology (Protopopescu *et al.*, 2005). The fMRI results in the present study were somewhat inconsistent with what we had predicted based on previous literature (Protopopescu *et al.*, 2005; St Jacques *et al.*, 2011). Explicitly, we had predicted amygdala responses to worst memories and their suppression under MDMA, but found neither. However, we did find effects that are somewhat consistent, namely attenuated activations to worst memories in a left anterior temporal cluster.

It is worth considering that at least some of the positively-biased emotional processing observed under MDMA in the present study may have been due to the tonic effects of MDMA rather than changes in induced responses. Indeed, to address this we compared ratings of general positive mood under MDMA with favourite memory-evoked positive affect and found a significant positive correlation ($p=0.032$, $R^2=0.19$). After this we looked to see whether positive mood under MDMA could explain the reduction in worst memory-evoked negative affect but there was no relationship ($R^2=0.025$). Thus, the tonic effects of MDMA may offer only a partial explanation of the evoked effects reported here. Resting state fMRI analyses may also be able to inform this matter further and this is something we are currently

investigating. Moreover, it is also possible that participants allowed their own positively-biased appraisals of MDMA to influence their subjective judgements; especially given that several were experienced users of MDMA. Contradicting this explanation however, we failed to find any correlations between extent of use and key outcomes such as the subjective responses during AMR.

The problem of underpowered designs in neuroscience, and specifically fMRI studies, has been highlighted recently (Button et al., 2013). The present study was the largest acute administration study of MDMA to date and was well-powered based on the outcomes of previous work (Bedi et al., 2009). It is especially difficult to conduct studies of this sort with controlled substances (Nutt et al., 2013), and despite our improved sample size relative to previous work neuroimaging work with MDMA, it remains possible that important effects went undetected. Future studies should note the relatively modest effects of MDMA on induced BOLD-responses observed here and sufficiently power for this.

The use of task-free rest as the condition against which emotional AMR was contrasted may be sub-optimal, as experimental control is essentially relinquished during the 'rest' state. An alternative strategy would be to compare activations to emotionally-potent AM cues with emotionally 'neutral' personal memory cues. However, participants may have found it particularly difficult to provide 'neutral' memory cues, since non-salient experiences are typically forgotten, and remembered experiences usually have at least some emotional and personal significance, even if this is implicit.

The lack of a behavioural index of task-performance means that we could not monitor whether subjects were performing the task as requested. It is difficult to incorporate a behavioural component into an AMR paradigm however as AMR relies on the evocation of a spontaneous process and is therefore naturally non-directive. Even so, the task could have been improved by including subjective ratings after each recollection rather than after the scanning session was complete. This may have improved the accuracy of the ratings and allowed some monitoring of task performance or compliance.

The study design could have been advanced by including varied doses of MDMA to test for dose-dependent effects on the primary outcomes. The inability to maintain the study blind was also a potential methodological weakness. It was important to compare the effects of MDMA against an inert placebo, so as to have a natural baseline; however, most of the volunteers noticed the drug effects and this may have biased outcomes. The incorporation of variable doses of MDMA may have helped to address this matter. Alternatively, future studies may consider comparing MDMA's effects against other psychoactive compounds, such as amphetamine.

It is also known that drugs that enter the brain can modulate neurovascular coupling and the hemodynamic

response function (Diukova et al., 2012) and it is possible that this could have accounted for the between-condition differences in BOLD responses reported here. However, MDMA's augmenting influence on favourite memories and attenuating effect on worst memories does not support this. Nevertheless, the study design could have been strengthened by incorporating measures specifically designed to address such potential confounds (Iannetti and Wise, 2007).

The inclusion of MDMA-experienced volunteers may also be viewed as a methodological limitation. The reported effects may have been different in MDMA-naïve individuals. Future work in MDMA-naïve individuals is encouraged, as this will improve the generalisability of the inferences that can be made on the study outcomes.

It is also advised that future studies look at potential modulatory effects of MDMA on behaviours that are specifically related to its unique profile of subjective effects (such as pro-social behaviours or the optimism bias) rather than more general cognitive processes that have less relevance to the acute MDMA state.

In summary, the present study found marked effects of MDMA on subjective responses to emotionally potent personal memories, specifically promoting the vividness, positivity and emotional intensity of favourite memories while attenuating the emotional negativity of worst memories and the drug was found to augment BOLD responses to favourite memories and attenuate responses to negative memories.

These results are broadly consistent with some previously demonstrated effects of pro-serotonergic manipulations on emotional processing (Harmer, 2008; Bedi et al., 2009). Future research is required to test the reliability of this study's findings, particularly in order to improve our understanding of how MDMA has such marked effects on emotional processing. Well-powered designs, with a focus on specific questions that incorporate more sophisticated pharmacological manipulations, e.g. selective receptor blockade, are advised.

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Conflict of Interest

The authors declare no conflict of interest.

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